

K083845

DEC 11 2009

510(K) SUMMARY

Cystic Fibrosis 60 kit v2

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirement of 21 CFR 807.92.

510(k) Number:

k083845

Purpose for Submission:

New Device.

Measurand:

CFTR (cystic Fibrosis transmembrane conductance regulator) gene from human blood specimens

Type of Test:

Qualitative nucleic acid multiplex test.

Applicant:

Luminex Molecular Diagnostics Inc.

439 University Ave.

Toronto, ON M5G 1Y8 Canada

Tel: 416.593.4323 x374

Fax: 416.593.1001

Contact person: Gloria Lee

Proprietary and Established Names:

xTAG® Cystic Fibrosis 60 kit v2

Regulatory Information:

1. Regulation Section:

21 CFR 866.5900, CFTR (cystic fibrosis transmembrane conductance regulator) gene mutation detection system

2. Classification:

Class II

3. Product Code:

NUA

4. Panel:

Immunology (82)

Intended Use:

The xTAG® Cystic Fibrosis 60 kit v2 is a device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in human blood specimens. The panel includes mutations and variants currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists (ACMG/ACOG) plus some of the world's most common and North American prevalent mutations. The xTAG Cystic Fibrosis 60 kit v2 is a qualitative genotyping test which provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children.

The kit is not indicated for use in fetal diagnostic or pre-implantation testing. This kit is also not indicated for stand-alone diagnostic purposes.

Indication(s) for use: same as intended use.

Special conditions for use statement(s):

The kit is not indicated for use in fetal diagnostic or pre-implantation testing. This kit is also not indicated for stand-alone diagnostic purposes.

Special instrument requirements:

Luminex 100 or 200 instrument

Device Description:

The xTAG CFTR 60 kit v2 includes the following components:

- xTAG PCR Primer Mix v2
- xTAG ASPE Mix A v2
- xTAG ASPE Mix B v2
- xTAG Bead Mix A v2
- xTAG Bead Mix B v2
- xTAG 10X Buffer
- Platinum® TFI Exo(-) DNA Polymerase
- Platinum® TFI Reaction Buffer, 5x
- TFI 50mM MgCl₂
- xTAG Shrimp Alkaline Phosphatase
- xTAG Exonuclease I
- xTAG Streptavidin-Phycoerythrin Conjugate

Substantial Equivalence Information:**1. Predicate device name(s):**

xTAG® Cystic Fibrosis kit

2. Predicate 510(k) number(s):

k043011, k060627

3. Comparison with predicate:

Parameter	xTAG Cystic Fibrosis 60 kit v2	xTAG Cystic Fibrosis kit
Intended Use	The xTAG Cystic Fibrosis 60 kit v2 is a device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in human blood specimens. The panel includes mutations and variants currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists (ACMG/ACOG), plus some of the worlds most common and North American-prevalent mutations.	The xTAG Cystic Fibrosis kit is a device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in human blood specimens. The panel includes mutations and variants currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists (ACMG/ACOG), plus some of the worlds most common and North American-prevalent mutations.
Indications for Use	The xTAG Cystic Fibrosis 60 kit v2 is a qualitative genotyping test which provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children.	The xTAG Cystic Fibrosis kit is a qualitative genotyping test which provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children.
Contra-Indications	The kit is not indicated for use in fetal diagnostic or pre-implantation testing. This kit is also not indicated for stand-alone diagnostic purposes.	The kit is not indicated for use in fetal diagnostic or pre-implantation testing. This kit is also not indicated for stand-alone diagnostic purposes.
Type of Test	Multiplex PCR followed by multiplex allele specific primer extension for genotyping, hybridized to multiplex fluorescent microparticles, detected by flow cytometry.	Multiplex PCR followed by multiplex allele specific primer extension for genotyping, hybridized to multiplex fluorescent microparticles, detected by flow cytometry.
Product Description	Tests for 60 mutations and 4 variants in the CFTR gene (23 of which are recommended by ACMG/ACOG).	Tests for 39 mutations and 4 variants in the CFTR gene (23 of which are recommended by ACMG/ACOG).
Specimen Type	Peripheral human whole blood.	Peripheral human whole blood.
Instrument System	Luminex 100 or 200 IS	Luminex 100 or 200 IS
Software	TDAS CFTR contains 1 template to detect mutations. Software masking function where user can chose to display results for only the ACMG / ACOG 23 mutations or the full panel of mutations.	TDAS CF-I contains 1 template to detect mutations.

Standard/Guidance Document Referenced (if applicable):

- American College of Medical Genetics (ACMG) / American College of Obstetricians and Gynecologists Technical Standards and Guidelines for CFTR Mutation Testing and Standards and Guidelines for Clinical Genetic Laboratories
- Cystic Fibrosis Foundation / Center for Disease Control Recommendations on Newborn Screening for CF
- FDA Class II Special Controls Guidance: Quality Control Material for Cystic Fibrosis Nucleic Acid Assays (Jan 2007)
- FDA Class II Special Controls Guidance: CFTR Gene Mutation Detection Systems (Oct 2005)
- CDRH Draft Guidance on Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns (Feb 2003)

- CDRH Draft Guidance on Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (Mar 2003)
- CDRH Guidance for the Content of Pre-Market Submission for Software Contained in Medical Devices (May 1998)
- CDRH Guidance on General Principles of Software Validation (Jan 2002)
- CDRH Guidance on Format for Traditional and Abbreviated 510ks (Aug 2005)
- MM01-A2: Molecular Diagnostic Methods for Genetic Diseases
- MM13-PE: Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods
- MM17-A: Verification and Validation of Multiplex Nucleic Acid Assays
- EP05-A2: Evaluation of Precision Performance of Clinical Chemistry Devices
- EP07-A2E: Interference Testing in Clinical Chemistry
- EP12-A: User Protocol for Evaluation of Qualitative Test Performance
- EP17-A: Protocols for Determining Limits of Detection and Limits of Quantitation

Test Principle:

The xTAG Cystic Fibrosis 60 kit v2 is comprised of a single multiplex PCR reaction which is then used in two separate ASPE reactions (A and B) and subsequently two separate bead hybridization reactions (A and B). DNA samples can be screened for 60 CFTR mutations and 4 variants (benign polymorphisms). The 'A' portion of the xTAG Cystic Fibrosis 60 kit v2 simultaneously screens for the 23 mutations and 4 variants currently recommended by ACMG/ACOG, plus 1078delT and 16 of the world's most common and North American-prevalent mutations. The 'B' portion of the xTAG Cystic Fibrosis 60 kit v2 simultaneously screens for 21 CFTR gene mutations.

To enable efficient incorporation of biotin-dCTP during the Allele Specific Primer Extension (ASPE) reaction, the PCR product is treated with Shrimp Alkaline Phosphatase (SAP) to inactivate remaining nucleotides (especially dCTP), and with Exonuclease I (EXO) to degrade any primers left over from the PCR reaction. Following SAP/EXO-treatment, a 5- μ L aliquot of the treated PCR product is used in each of the ASPE 'A' and 'B' reactions. Each ASPE reaction product is sorted by hybridization to the universal array (Bead Mix A and B) in the presence of hybridization buffer, and then incubated with Streptavidin, R-Phycoerythrin conjugate (reporter solution). Samples are read on the Luminex® 100/200 analyzer and fluorescence values captured in the Output.csv files are analyzed by the xTAG Data Analysis Software (TDAS CFTR).

For each sample analyzed by the xTAG Cystic Fibrosis 60 kit v2, an output file containing MFI signals from the Luminex instrument is generated. The proprietary software component of this product analyzes this output data file, to provide a final qualitative genotype for the sample. The user must select between 2 options for the final output prior to running the assay:

Option 1: Full Panel (60 mutations/deletions + 4 variants).
 Option 2: ACMG/ACOG panel (23 mutations and deletions).

Performance Characteristics (if/when applicable):

Clinical Performance Characteristics:

a) Method Comparison Studies / Accuracy:

Accuracy of the xTAG CFTR 60 kit v2 was assessed through evaluation of samples representing all alleles (mutations and polymorphisms) probed by the assay. The majority of samples consisted of left-over, anonymized, banked whole-blood specimens. These specimens were supplemented with genomic DNAs from EBV-transformed lymphoid cell lines, and several custom-designed plasmids engineered to contain 1-2 CFTR mutations each. Archived clinical genomic DNA samples were obtained from a variety of sources.

The FDA cleared xTAG Cystic Fibrosis Kit (k043011 and k060627) was used as the comparator for the panel A mutations and dideoxy-sequencing was used for the panel B mutations.

A total of 488 mutant alleles was tested over a total of 396 clinical samples. Some of the clinical samples were compound Hets or homozygous mutants. The xTAG Cystic Fibrosis 60 kit v2 demonstrated 100% accuracy after allowable re-runs.

Analytical Performance Characteristics:

a) Precision/Reproducibility:

A multi-centre, multi-operator, multi-lot, blinded study design was used to evaluate total variability of the xTAG Cystic Fibrosis 60 kit v2.

The reproducibility of the analytical (post-extraction) steps of the assay was evaluated at 3 independent sites using in order of preference and availability, purified genomic DNAs extracted from clinical (whole blood) samples, purified genomic DNA extracted from lymphoid cell lines, and/or plasmids. Each set of samples contained samples representing all mutations and variants probed by the xTAG Cystic Fibrosis 60 kit v2. There were 2 operators per site, each performing 1 run / day across 3 non-consecutive days (3 runs per operator or 6 runs per site). Within a given run, each assay point was run in duplicate. A total of three (3) assay lots were tested (1 lot / site).

Across sites, operators: The xTAG Cystic Fibrosis 60 kit v2 assay detected all 60 mutations, as well as normal (wild-type) alleles, with a precision of > 99.99% after allowable re-runs across 3 sites, between 6 operators (2 per site) and between reagent lots (a total of 3 lots, 1 lot per site). Two samples (Coriell genomic DNA) made a 'No Call' after an allowable rerun at Site 3 (operator 1) whereas one plasmid sample made 3 miscalls at Site 1 between 2 operators. Reproducibility of detection of a compound heterozygote dF508 / F508C was also characterized in this study. Of the 36 replicates of a sample tested, 30 generated a dF508 HET call and 6 generated a dF508 Mu D call. Both results are accurate when taking into consideration the definition of a Mu D call (i.e. only the mutant allele is detected).

Per sample: The xTAG Cystic Fibrosis 60 kit v2 assay detects mutant / variant / wild-type alleles of the 60 loci assayed with reproducibility (after allowed reruns) of 91.67% for allele 2307insA, 99.57% for allele dF508mut, and 100.00% for the remaining 58 alleles. For reproducibility testing of the 2307insA allele, a plasmid DNA was used. In 3 out of 36 test points this sample was detected as a HET instead of a Mu D however, in the accuracy study, all clinical samples representing the 2307insA mutation (2 Whole Blood DNA and 1 Blood Spot DNA) were correctly identified by this assay.

b) Traceability, Stability, Expected Values (controls, calibrators, or methods):

N/A

c) Detection Limit and range of assay:

Genomic DNA samples representing a subset of mutations in the CFTR 60 kit v2 test were assayed at the following concentrations: 300, 150, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78 and 0.39 ng/µL. Each sample was run in duplicate. Genomic DNA, extracted from whole blood, was used as a wild-type positive control in all runs. At each tested concentration, the data across all samples were pooled. The lowest concentration giving an apparent assay failure rate of $\leq 5\%$ was considered an estimator of the LoD. The proposed assay lower bound (LB) was set at a concentration (C*) lying at or slightly above the estimated LoD. At concentration C*, 22 replicates of each of the 10 genomic DNAs were run along with 8 negative controls dispersed uniformly throughout the plate to determine the LoD. The Lower Bound and Upper Bound of the assay range was determined to be 2 ng/µL and 300 ng/µL, respectively. The LoD was determined to be 1.56 ng/µL.

d) Analytical Specificity / Interfering Substances:

An Interference study was conducted to examine the effects of potential interferents that might be expected to be found in whole blood samples (1500 µg/mL hemoglobin, 200 µg/mL bilirubin, and 30 mg/mL mixture of triglycerides). Eight whole blood samples were split into 6 parts each, and incubated either in the absence or presence of one of the 3 potential interferents, extracted and assayed with CFTR 60 kit v2. No difference was observed between the final qualitative calls made from the untreated vs treated samples. This study showed that none of the potential interferents commonly found in whole blood produced a significant inhibitory effect on the performance of the CFTR 60 kit v2.

e) Assay Cut-off:

N/A



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

Luminex Molecular Diagnostics, Inc.
c/o Gloria Lee, Ph.D.
Manager, Regulatory Affairs
439 University Avenue, Suite 2000
Toronto, Ontario
Canada M5G 1Y8

DEC 11 2009

Re: k083845

Trade/Device Name: xTAG® Cystic Fibrosis 60 Kit v2

Regulation Number: 21 CFR §866.5900

Regulation Name: CFTR (cystic fibrosis transmembrane conductance regulator) gene mutation detection system

Regulatory Class: Class II

Product Code: NUA

Dated: December 8, 2009

Received: December 9, 2009

Dear Dr. Lee:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21

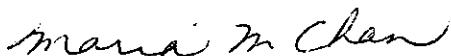
Page 2 – Gloria Lee, Ph.D.

CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOFFICES/ucm115809.htm> for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address <http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>.

Sincerely yours,



Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): k083845

Device Name: xTAG® Cystic Fibrosis 60 kit v2

Indications For Use:

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Prescription Use X AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF
NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Reena Philip
Division Sign-Off

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Office of In Vitro Diagnostic Device
Evaluation and Safety

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